DELETION OF INVENTORS

Please correct the inventorship under 37 CFR §1.48(b) by removing the following inventors from the present application:

Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen, and Colin K. Watanabe.

REMARKS

Applicants have cancelled Claims 1-3 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claim 4 to be in independent form, and have amended Claims 5 and 12 to depend from Claim 4. Claim 13 is amended to replace the term "epitope tag" with the term "tag polypeptide." New Claims 14-17 have been added. Thus, Claims 4-17 are presented for further examination.

Applicants submit that no new matter was added by the amendments, and that support for the amendments can be found throughout the specification. Support for the amendments to Claim 13 can be found, for example, at paragraph [0229]. Support for new Claims 14-17 can be found, for example, in the claims as originally filed and paragraphs [0336], [0362], [0407], and Example 18 starting at paragraph [0529].

Correction of Inventorship under 37 CFR §1.48(b)

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Objections to the Specification

The Examiner objected to the specification because it contains an embedded hyperlink and/or other form of browser-executable code on page 31, paragraph 205.

Applicants have amended the specification to address the Examiner's concern. In particular, Applicants have replaced the hyperlink with text that describes the location of the website. The amended text no longer constitutes browser executable code.

Information Disclosure Statement

The information disclosure statement submitted on 10 September 2002 was considered by the examiner. However, the Examiner states that since the Blast results cited therein are not true publications with a publication date, they will not be printed on the face of the patent issuing

from this application. Applicants submit a listing including the publication dates of the sequences found in the BLAST search with the Information Disclosure Statement provided herewith.

Indefiniteness

Claims 1-6, 9-10, 12-13 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite in view of the limitations that the claimed protein lacks its associated signal peptide or comprises an "extracellular domain" optionally lacking its associated signal peptide. According to the Examiner, these limitations are indefinite because neither the figure (Figure 14) nor the specification define or teach the metes and bounds of the extracellular domain. Further, according to the Examiner, if the protein has an extracellular domain, the recitation of "extracellular domain"..."lacking its associated signal sequence" is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of protein production in the cell. The Examiner asserts that Figure 14 provides no written description of the extracellular domain(s).

The features described in Figure 14 for SEQ ID NO: 14 indicate that there is a signal peptide at amino acids 1-20, transmembrane domains at amino acids 54-72, 100-118, 130-144, and 146-166, and myristoylation sites at amino acids 14-20, 78-84, 79-85, 202-208 and 217-223. Accordingly, the extracellular domains lie at amino acids 21-53, 119-129, and 167-234. Applicants have amended the claims to provide the locations of the extracellular domains. In the interest of advancing prosecution of this application, Applicants will acquiesce to the PTO's assertion that a signal peptide is not normally considered part of the extracellular domain. By making this concession, Applicants understand that element (c) of Claims 4-6 describes a polypeptide comprising the extracellular domain of the polypeptide of SEQ ID NO: 14, **lacking** its associated signal peptide. At the same time, as amended, element (d) of Claims 4-6 describes a polypeptide comprising the extracellular domain of the polypeptide of SEQ ID NO: 14, **including** its associated signal peptide. Applicants state that this argument is made only in connection with the instant application, and does not reflect the Applicants' interpretation of any claims in any related applications.

Claim 13 was rejected on the assertion that it is indefinite for reciting "epitope tag" because the exact meaning of the phrase is not clear. The Examiner asks whether the phrase means an "epitope" where an antibody binds or a tag that allows for purification that is an amino acid sequence that does not require binding to an antibody, or some other tag. Claim 13 has been amended to recite "a tag polypeptide." As recited in the specification at [0229], a tag polypeptide comprises a polypeptide against which an antibody can be made.

Utility

Claims 1-13 were rejected under 35 U.S.C. 101 on the assertion that the claimed invention is not supported by either a substantial asserted utility or a well established utility. The Examiner asserts that the specification does not disclose that the polypeptide has any homology with known, characterized polypeptides or any additional information regarding PRO1864 such as subcellular location, timing of regulation during cellular differentiation, which hormones or transcription factors regulate PRO1864, and what physiological significance PRO1864 plays. Therefore, it is a totally new, uncharacterized polypeptide with no well-established utility.

The Examiner asserts that the use of the claimed PRO polypeptide to isolate other polypeptides to which it binds (paragraph 0329 of the specification) is not specific or substantial. According to the Examiner, since the same can be done with any polypeptide, the asserted utility is not specific to the claimed PRO1864 polypeptides. Furthermore, the Examiner asserts that since the specification does not disclose how PRO1864 or its binding partners can be used, significant further research would be required of the skilled artisan to determine how to use the claimed polypeptide or its binding partner. According to the Examiner, since the asserted utility is not presented in a ready to use, real-world application, the asserted utility is not substantial.

The Examiner asserts that the use of the claimed PRO polypeptides as a molecular weight marker (paragraph 0334 of the specification) is not specific. According to the Examiner, since the same can be done with any polypeptide, the asserted utility is not specific to the claimed PRO1864 polypeptides.

The Examiner asserts that the use of the claimed PRO polypeptides in tissue typing (paragraph 0336 of the specification) is not specific or substantial. According to the Examiner,

with the exception of a few housekeeping genes, all polypeptides have a tissue specific pattern of expression, and thus virtually any polypeptide can be used in tissue typing.

The Examiner asserts that the use of the claimed PRO polypeptides in therapy (paragraph 0337 of the specification) is not specific or substantial. According to the Examiner, since a defect in any polypeptide is likely to cause a disease of some sort, every polypeptide is a target for drug development. Thus, the Examiner maintains that the asserted utility is not specific to the claimed PRO1864 polypeptide. Furthermore, the Examiner asserts that the specification does not disclose a nexus between any specific disease states and a change in amount or form of PRO1864. Significant further research would have to be conducted to identify such a nexus. Therefore, the asserted utility is not substantial.

The Examiner asserts that the use of the claimed PRO polypeptides to identify agonists or antagonists is not specific since the same can be done with any polypeptide. Furthermore, the Examiner asserts that since no activity has been assigned to PRO1864, the assays cannot be conducted until the specific biological activities of PRO1864 are determined empirically. According to the Examiner, the asserted utility is also not substantial.

The Examiner asserts that the determination that PRO1864 is overexpressed in certain tumors does not provide a credible, specific and substantial utility for PRO1864 nucleic acids, polypeptides or antibodies. According to the Examiner, the data is not presented to indicate such overexpression or how it was determined. The Examiner asserts that this is very vague, and does not disclose what mathematical calculations were used to establish significance. Therefore, according to the Examiner, the data presented in the microarray assay are preliminary at best, and cannot be evaluated or repeated independently by the skilled artisan. Clearly, further research would be required of the skilled artisan to establish whether and how a probe used in the microarray assay could be used as diagnostic markers or therapeutic targets. The Examiner asserts that such further experimentation indicates that the asserted utility is not in currently available form.

Furthermore, the Examiner asserts that the literature indicates that such results are to be evaluated very critically. The Examiner cites Hu et al. (2003. Journal of Proteome Research 2:405-412) as showing that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role

in the disease. However, the Examiner acknowledges that among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

The Examiner cites Haynes et al. (1998, Electrophoresis 1921862-1871) for the proposition that increased transcription does not always correlate with increased polypeptide levels. The Examiner states that Haynes et al. studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances, which varied more than 50-fold. Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Therefore, the art indicates that it is not the norm that increased transcription results in increased polypeptide levels.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "[T]o violate § 101 the claimed device must be totally incapable of achieving a useful result" *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed.Cir.1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained either because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. M.P.E.P. § 2107.02 III B. (underline emphasis in original, bold emphasis added); citing *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the

art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured change in gene expression in cancer cells establishes a "significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween."

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed polypeptides have utility as diagnostic tools and therapeutic agents for cancer, particularly melanoma. With respect to the use of the claimed polypeptides as diagnostic tools, Applicants are not asserting that the claimed polypeptides necessarily provide a definitive diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools to assist in the diagnosis of certain cancers. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1864 polypeptide is more highly expressed in melanoma compared to normal skin tissue;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA encoding a particular protein, e.g. an increase, generally leads to a corresponding change in the level of the encoded protein, e.g. an increase;

3. Given Applicants' evidence that the level of mRNA for the PRO1864 polypeptide is increased in melanoma compared to normal skin tissue, it is likely that the PRO1864 polypeptide is differentially expressed in melanoma and is therefore useful as a diagnostic tool to distinguish tumor from normal tissue and as a therapeutic target.

Applicants understand the PTO to be making several arguments regarding the utility of the claimed polypeptides:

1. The PTO asserts that the significance of the evidence reported in Example 18 is unclear;

2. The PTO states that increased transcription does not always correlate with increased polypeptide levels;

3. The PTO asserts that the asserted utilities are not specific to the claimed polypeptides.

As detailed below, Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Applicants maintain that the PTO has failed to offer any evidence to support its rejection of the data in Example 18. Applicants submit that given the well-established correlation between a change in the level of mRNA with a corresponding change in the levels of the encoded protein, the PRO1864 protein is likely differentially expressed in certain tumors. Finally, Applicants maintain that because the claimed polypeptides have been shown to be differentially expressed in melanoma, a property not shared by all polypeptides, the claimed polypeptides have specific utility.

Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence to establish that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not statistical or absolute certainty.**

Applicants have established that the Gene Encoding the PRO1864 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Applicants first address the PTO's argument that the evidence of differential expression of the gene encoding the PRO1864 polypeptide in melanoma is insufficient. The Examiner maintains that the data presented in Example 18 are preliminary at best, and cannot be evaluated or repeated independently by the skilled artisan. The PTO argues that Example 18 is vague, does not disclose what mathematical calculations were used to establish significance or what the

significance actually is, or how one would use such significance in diagnosing the presence or absence of tumor in a subject or how one would use such significance as a therapeutic target.

Applicants maintain that the data in Example 18 are sufficient to establish that the mRNA encoding the PRO1864 polypeptide is more highly expressed in melanoma compared to normal skin. Gene expression was analyzed using standard semi-quantitative PCR amplification reactions of cDNA libraries isolated from different human tumor and normal human tissue samples. Identification of the differential expression of the PRO1864 polypeptide-encoding gene in tumor tissue compared to the corresponding normal tissue renders the molecule useful as a diagnostic tool for the determination of the presence or absence of tumor and as a therapeutic target. Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (attached as Exhibit 1) This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue (see Declaration, paragraph 7).

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

The use of pooled samples increases the accuracy of the experiment. In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples.

In addition, Applicants note that Dr. Grimaldi also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). The PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his statements. Mr. Grimaldi has personal knowledge of the relevant facts, has based his statements on those facts, and the PTO has offered no reason or evidence to reject either the underlying facts or his statements. Therefore, the PTO should accept Mr. Grimaldi's statements establishing that there is at least a two-fold difference in expression, and that the results are reliable enough that they can be used to distinguish tumor from normal tissue.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration, establishes that there is at least a two-fold difference in PRO1864 cDNA between melanoma and normal skin tissue.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA for a particular

protein, generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1864 polypeptide in melanoma, it is more likely than not that the PRO1864 polypeptide is differentially expressed; and proteins differentially expressed in certain tumors have utility as diagnostic tools and therapeutic targets. Applicants submit herewith as Exhibit 2 a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 3), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 4) and (4th ed. 2002) (submitted herewith as Exhibit 5)). Figure 9-2 of Exhibit 4 shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 4 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 4 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 4 at 453 (emphasis added). Thus, as established in Exhibit 4, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 5, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Exhibit 5 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 5 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Exhibit 5 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Exhibit 5 at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted herewith as Exhibit 6) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, submitted herewith as Exhibit 7. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression." Exhibit 7 at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 7 at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." Exhibit 7 at 7.

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 8, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

The Examiner cited Haynes et al. (1998, Electrophoresis 192:1862-1871) as showing that there is no strong correlation between protein and transcript level. The Examiner asserts that the art indicates that it is not the norm that increased transcription results in increased polypeptide levels.

Applicants submit that Haynes does not contradict the utility or enablement of the instant claims. Haynes is a review article dealing with the art of proteome analysis. The assertions in Haynes cited by the Examiner were made in an effort to identify shortcomings in the art of mRNA quantification to argue for "proteome analysis to become an essential component in the comprehensive analysis of biological systems." Haynes, p. 1863. Haynes studied 80 selected samples from *Saccharomyces cerevisiae*, and reported "a general trend but no strong correlation between protein and transcript levels (Fig. 1)." Id. However, a cursory inspection of Fig. 1 shows a clear correlation between the mRNA levels and protein levels measured. This correlation is confirmed by an inspection of the full-length research paper from which the data in Fig. 1 were derived, presented herein as Exhibit 9 (Gygi et al., Molecular and Cellular Biology, Mar. 1999, 1720-1730). Gygi states that "there was a general trend of increased protein levels resulting from increased mRNA levels," with a correlation coefficient of 0.935, indicating a strong correlation. Gygi, p. 1726. Moreover, Gygi also states that the correlation is especially strong for highly expressed mRNAs. Id. Considering that Example 18 of the specification shows higher expression of PRO1864 mRNA in melanoma compared to normal skin tissue, Haynes and Gygi actually provide strong evidence in support of a general correlation between mRNA and protein levels.

The 50-fold variation referred to by Haynes and cited by the Examiner, does not in any way show the absence of a correlation between mRNA and protein levels, but rather identifies the outer limits of variability in the authors' experiments. This variability may support the authors' assertion that the amount of a particular protein cannot accurately predict the particular level of the corresponding mRNA transcript, but it does not suggest an absence of a general correlation between mRNA and protein levels. Again, Applicants' utility is based on the differential expression of mRNA in normal skin tissue versus melanoma. Exact levels of expression are irrelevant. Moreover, Gygi states that the high degree of variability seen at low levels of mRNA (shown in inset of Fig. 1, Haynes p. 1863) is due to the fact that "the magnitude of the error in the measurement of mRNA levels is inversely proportional to the mRNA levels." Gygi, p. 1727. Considering that PRO1864 mRNA has been shown in Example 18 of the specification to be more highly expressed in melanoma than normal skin tissue, the variability

identified by Haynes is even less applicable to establishing the absence of a correlation between mRNA and protein levels in the instant case.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. As discussed above, Applicants maintain that it is more likely than not that the PRO1864 polypeptide is differentially expressed. Applicants note that the utility requirement does not require Applicants to show that mRNA levels correlate to protein levels in every case. The data presented in Haynes is not inconsistent with or contradictory to the utility or enablement of the instant claims. To the contrary, the data clearly show a general correlation between protein levels and mRNA levels, and thus support Applicants' assertion that such a general correlation exists.

Even if Haynes supported the Examiner's argument, which it does not, one contrary example does not establish that one of skill in the art would find it is more likely than not there is no general correlation between mRNA level and protein levels. In fact, the working hypothesis among those skilled in the art, as illustrated by the evidence presented herein by Applicants, is that there is a direct correlation between mRNA levels and protein levels. This is further supported by the statement in Haynes that "interpretations of quantitative mRNA expression profiles frequently implicitly or explicitly assume that for specific genes the transcript levels are indicative of the levels of protein expression." See, Haynes, p. 1863, first full paragraph. Haynes does not suggest there is no correlation between mRNA and protein levels, but rather points to what the authors believe are shortcomings of using mRNA quantification to predict protein levels; specifically, that mRNA levels may not accurately predict protein levels *in each particular instance*. Considering the more likely than not standard for utility, Haynes' identification of reasons why proteomic analysis may be preferable in some cases does not contradict Applicants' evidence that there is a general correlation between mRNA and protein levels.

The Examiner cited Hu et al. (2003, Journal of Proteome Research 2:405-412) as showing that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. The Examiner acknowledges that Hu shows that, among genes with a 10-fold or more

change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section of Hu et al.).

As an initial matter, Applicants submit that whether or not PRO1864 is the causative agent for melanoma does not impact its use as a diagnostic tool for cancer. One does not need to know why PRO1864 is differentially expressed, or what the consequence of the differential expression is, in order to exploit the differential expression to distinguish tumor from normal tissue. In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. (*See* the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming differentially expressed polypeptides. (*See, e.g.,* U.S. Patent No. 6,414,117 and U.S. Patent No. 6,124,433, attached hereto as Exhibits 10 and 11.)

With respect to the Hu publication cited by the Examiner, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the

greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker. Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease.

The Claimed Polypeptides would have Diagnostic Utility even if there is no Positive Correlation between Gene Expression and Expression of the Encoded Polypeptide

Even assuming *arguendo* that, there is no direct correlation between gene expression and protein expression for PRO1864, which Applicants submit is not true, a polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 2, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 12), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate

tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin (attached as Exhibit 13). The article teaches that the HER-2/neu gene has been shown to be amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, a polypeptide encoded by a gene that is differentially expressed in cancer would still have utility. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed polypeptides.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

The PTO has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that the disclosed polypeptide is differentially expressed in certain tumors and that the claimed polypeptides can be used as diagnostic tools. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed polypeptides can be used as diagnostic tools for cancer, particularly melanoma.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Polypeptides

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed polypeptides related to PRO1864. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1864 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed polypeptides.

As discussed above, there are significant data which show that the gene for the PRO1864 polypeptide is more highly expressed in melanoma compared to normal skin tissue. These data are strong evidence that the PRO1864 gene and polypeptide are associated with melanoma. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1864 gene and polypeptide with a specific disease. The asserted utility as a

diagnostic tool and therapeutic target for cancer, particularly melanoma, is a specific utility – it is not a general utility that would apply to the broad class of polypeptides.

Conclusion

The PTO has asserted several arguments to support its conclusion that the differential expression of PRO1864 mRNA is not sufficient to establish utility for the claimed polypeptides:

1. The PTO asserts that the significance of the evidence reported in Example 18 is unclear;

2. The PTO states that increased transcription does not always correlate with increased polypeptide levels;

3. The PTO asserts that the asserted utilities are not specific to the claimed polypeptides.

Applicants have addressed each of these arguments in turn.

First, the Applicants provided a first Declaration of Chris Grimaldi stating that the data in Example 18 are real and significant. This declaration also indicates that given the relative difference in expression levels, the disclosed nucleic acids and corresponding polypeptides have utility as cancer diagnostic tools.

Second, Applicants have shown that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in the encoded protein levels.

Applicants have also presented the declarations of two experts in the field, which establish that even in the anomalous case where there is no positive correlation between gene expression and expression of the encoded protein, the simultaneous monitoring of both is useful for diagnosis and further classification of the cancer.

Applicants have pointed out that the substantial utilities described above are specific to the claimed polypeptides because the PRO1864 gene is differentially expressed in melanoma cells compared to normal skin tissue. This is not a general utility that would apply to the broad class of polypeptides.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed polypeptides as diagnostic tools.

According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed polypeptides set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Written Description

Claims 1-5 and 12-13 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. According to the Examiner, the claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the Examiner asserts that the claims are drawn to a genus of polypeptides that is defined only by sequence identity. The Examiner asserts that in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. The Examiner asserts that only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO:14, but not the full breadth of the claim meets the written description provision of 35 U.S.C. § 112, first paragraph.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

As amended, the pending claims are related to isolated polypeptides having at least 95% or 99% amino acid sequence identity to several polypeptides related to SEQ ID NO: 14, and satisfy the limitation "wherein said isolated polypeptide is more highly expressed in melanoma compared to normal skin tissue, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in melanoma compared to normal skin tissue" or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody

which can be used to specifically detect the polypeptide of SEQ ID NO: 14 in skin tissue samples."

Applicants maintain that there is not substantial variation within the species which fall within the scope of the amended claims, which require at least 95% or 99% amino acid sequence identity to the disclosed sequences related to SEQ ID NO: 14. Applicants note that the pending Claims are analogous to the claims discussed in Example 14 of the written description training materials. In Example 14, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, the pending claims also have very high sequence homology to the disclosed sequences and must share the same expression pattern in certain tumors, or share an epitope sufficient to generate antibodies which specifically detect the polypeptide of SEQ ID NO: 14 in skin tissue samples.

In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make polypeptides with at least 95% amino acid sequence identity to the disclosed sequences. In addition, the specification discloses how to test to determine if the polypeptide or encoding nucleic acid is differentially expressed in melanoma, and how to make antibodies which specifically detect the polypeptide of SEQ ID NO: 14 in skin tissue samples. Like Example 14, the genus of polypeptides that have at least 95% or 99% amino acid sequence identity to the disclosed sequences will not have substantial variation.

Furthermore, while Applicants appreciate that actions taken by the PTO in other applications are not binding with respect to the examination of the present application, Applicants note that the PTO has issued many patents containing claims to variant nucleic acids or variant proteins where the applicants did not actually make such nucleic acids or proteins. Representative patents include U.S. Patent No: 6,737,522, U.S. Patent No. 6,395,306, U.S. Patent No. 6,025,156, U.S. Patent No. 6,645,499, U.S. Patent No. 6,498,235, and U.S. Patent No. 6,730,502 which are attached hereto as Exhibits 14-19.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO: 14, by specifying a high level of amino acid sequence identity, by describing how to test for

differential expression of the polypeptide and encoding nucleic acid, and by describing how to make antibodies to the disclosed sequence, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Claims 1-6, 11-13 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner objected to the specification under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials. According to the Examiner, the specification lacks complete deposit information for the deposit of the cell line containing cDNA deposited under ATCC accession No. 203579. The Examiner asserts that it is not clear that the cDNA deposited as ATCC no. 203579 is known and publicly available or can be reproducibly isolated from nature without undue experimentation or is the same as SEQ ID NO:13 or encodes SEQ ID NO:14 or contains additional sequences in addition to SEQ ID NO:14. The Examiner also asserts that Applicant's referral to the deposit of the cDNA on page 121 of the specification is an insufficient assurance that the required deposit has been made and all the conditions of 37 CFR 1.801-1.809 met. The Examiner notes that this requirement can be satisfied if the deposit is made under the provisions of the Budapest Treaty by filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application.

In response to the above rejection relating to the biological deposit, Applicants submit a statement under 37 C.F.R. §1.808 containing the language recommended by the Examiner.

Enablement

Claims 1-13 were also rejected under 35 U.S.C. §112, first paragraph. Specifically, the Examiner asserts that since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention.

As discussed above, the claimed invention satisfies the utility requirement of 35 U.S.C. §112, first paragraph. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Claims 1-5, 12-13 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner asserts that there is no functional limitation in the claims as far as to the polypeptide and that the specification does not teach that the polypeptide is over expressed in any disease state and does not teach an activity for the polypeptide or any active regions of the polypeptide. Thus the Examiner asserts that one would not know if the polypeptide with the claimed homology would function as a polypeptide of SEQ ID NO:14.

The Examiner also asserts that the claims encompass an unreasonable number of inoperative polypeptides, which the skilled artisan would not know how to use. According to the Examiner, there are no working examples of polypeptides less than 100% identical to the polypeptide SEQ ID NO: 14 or the mature form thereof. The Examiner asserts that a skilled artisan would not know how to use non-identical polypeptides on the basis of teachings in the prior art or specification. According to the Examiner, even if the claimed polypeptides had a function, the specification does not provide guidance for using polypeptides related to (i.e., 80%-99% identity) but not identical to SEQ ID NO:14. The Examiner asserts that the claims are broad because they do not require the claimed polypeptide to be identical to the disclosed sequence and because the claims have no functional limitation.

The Examiner further asserts that it is well known in the art that even a single modification or substitution in a protein sequence can alter the proteins function. The Examiner cites Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138, Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252, Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987) and Un et al Biochemistry USA Vol 14:1559-1563 (1975) in support of this proposition. According to the Examiner, these references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

As discussed above, Applicants maintain that there is not substantial variation within the species encompassed by the pending claims and that the present situation is analogous to Example 14 of the written description training materials. Furthermore, Applicants maintain that the determination of whether a polypeptide is more highly expressed in melanoma compared to normal skin tissue, whether a polypeptide is encoded by a polynucleotide which is more highly expressed in melanoma compared to normal skin tissue, or whether an isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect a polypeptide in skin tissue samples involves routine methodology such as Western Blotting, Northern Blotting or PCR. The implementation of routine techniques does not constitute undue experimentation. (See *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). Accordingly, the specification enables one skilled in the art to make and use the claimed invention.

The Examiner asserts that the specification does not disclose that the protein is overexpressed in any disease state. According to the Examiner, those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression. The Examiner asserts that evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels. Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) is cited as teaching that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Powell et al (Pharmacogenesis, 1998, Vol. 8, pp. 411-421, abstract) is cited as teaching that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein, and that the regulation of said protein is highly complex. Vallejo et al (Biochimie, 2000, vol. 82,

pp. 1129-1133, abstract) is cited as teaching that no correlation was found between NRF-2 mRNA and protein levels suggesting post-transcriptional regulation of NRF-2 protein levels. According to the Examiner, these references serve to demonstrate that the analysis of levels of polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression.

The Examiner's rejection is based on concerns similar to those addressed in response to the rejections asserting lack of utility which were addressed above. As discussed above, in view of the differential expression of the mRNA encoding the polypeptide of SEQ ID NO: 14 in melanoma, it is more likely than not that this polypeptide is differentially expressed. The Examiner's citation of Vallejo, Powell, Jang, and Fu as examples of particular genes for which the levels of mRNA do not correlate with the level of the corresponding proteins does not rebut this evidence, but rather provides examples of post-transcriptional modification, the existence of which is acknowledged by Applicants. As discussed above, the Genes VI textbook provides that, "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." (Genes VI, Benjamin Lewin, 1997, Chapter 29 – Regulation of Transcription, 1st page). Further, Lewin goes on to state that transcription of a gene "is a major control point: probably **it is the most common level of regulation**." Id., emphasis added. This reference, and the additional references discussed above, provide additional support for Applicants' position that that the accepted understanding in the art is that there is a *reasonable* correlation between gene expression and the level of the encoded protein.

The Examiner cites Vallejo et al., Powell et al., and Fu et al. for the proposition that there is no correlation between mRNA and protein levels for particular genes. While these references may provide actual examples of post-transcriptional regulation of protein levels, they are not inconsistent with Applicants' position that mRNA levels correlate, more often than not, with protein levels. Applicants do not assert that post-transcriptional regulation never occurs, and furthermore need not establish that a correlation between mRNA and protein levels always exists. In light of the controlling standard for establishing utility, Applicants need only show that a correlation between mRNA and protein levels more likely than not exists in the eyes of those

skilled in the art, making it more likely than not that levels of PRO1864 mRNA are indicative of the levels of PRO1864 polypeptides.

Applicants respectfully submit that the great weight of the evidence supports the conclusion that it is more likely than not that the claimed polypeptides are differentially expressed. In the above response to the rejection asserting lack of utility, Applicants have provided numerous examples demonstrating a general understanding in the art that protein levels are regulated primarily by regulating mRNA levels in the large majority of cases, including the statements in Alberts and Lewin, leading textbooks in the field of Molecular Biology, and the declarations of Dr. Polakis and Dr. Grimaldi, both experts in the field of Cancer Biology with numerous years of experience. Of particular significance is the fact that these references have identified the general understanding in the field, as opposed to isolated examples. In addition, the experiments testified to by Dr. Polakis as well as those in Haynes show a correlation between mRNA and protein levels for a large number of different genes. These references are in addition to the numerous examples of particular genes shown by Applicants, including those in Example 18 of the specification, and in the references submitted in the accompanying Exhibits. Applicants respectfully submit that the totality of the above-cited evidence clearly establishes that those of skill in the art would believe, more likely than not, that mRNA levels correlate with protein levels. The Examiner's citation of Vallejo, Powell, and Fu as examples of particular genes for which the levels of mRNA do not correlate with the level of the corresponding proteins does not rebut this evidence, but rather provides examples of post-transcriptional modification, the existence of which is acknowledged by Applicants. In light of the fact that Applicants need not show a *necessary* correlation between mRNA and protein levels, Applicants respectfully submit that they have rebutted any prima facie case of non-utility or non-enablement which the Examiner may have established. In fact, the "more likely than not" standard would effectively be an "absolute certainty" standard if the Examiner's few instances of post-transcriptional regulation were found to establish the non-existence of a general correlation between mRNA and protein levels in light of the totality of evidence produced above by Applicants.

The Examiner cites Pennica et al (PNAS 95:14717-22,1998) as teaching that the copy number is amplified but the RNA expression is actually reduced. Applicants respectfully submit that the PTO is confusing the relationship between an increase in copy number of a gene or gene

amplification on the one hand, and increased expression of a gene or mRNA expression on the other. Pennica provides that the *WISP-2* gene DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient. (Pennica, page 14722) This result may not even be real, as the authors explain: "Because the center of the 20q13 amplicon [of which *WISP-2* is a part] has not yet been identified, it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon." Pennica at 14722 (emphasis added).

However, even if the lack of correlation between DNA copy number and mRNA level in Pennica is real, Pennica says nothing about a lack of correlation between the level of mRNA and the level of protein expression – Pennica did not even look at protein expression. It is the correlation between mRNA level, as assessed by probing the cDNA library, and the level of protein expression which is at issue here, not the correlation of gene copy number and mRNA levels. The data Applicants report in Example 18 indicate that there are more copies of the mRNA encoding the polypeptide of SEQ ID NO: 14 in melanoma than normal skin tissue. Nothing in Pennica is contrary to Applicants' assertion that it is well-established in the art that the level of protein is positively correlated to the level of mRNA.

As stated above, it is more likely than not that the claimed polypeptides are differentially expressed in melanoma. Even if Pennica supported the PTO's argument, which it does not, one contrary example does not establish that one of skill in the art would find it is more likely than not, that in general, there is no correlation between mRNA level and protein levels. In fact, as discussed above, the working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels.

Further, Jang et al (Clinical and Experimental Metastasis, 1997, vol. 15, pp. 469-483, abstract) is cited as teaching that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing further evidence that one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification. Jang subjected tumor cells to growth stress conditions, and then measured mRNA and protein expression levels

during and after recovery to ascertain whether a particular set of genes exhibited changes in expression in response to the stressed conditions. See, Jang, Abstract. The key point with regard to the present case is that Jang did not report measurements of the correlation between mRNA and protein levels. Instead, Jang measured correlations between the metastatic potential of the cells after recovery and the level of either mRNA or protein, to determine whether changes in the metastatic potential could be attributed to particular genes/proteins. Id. The statement cited by the Examiner does not imply that the reason additional research is needed is because the levels of mRNA and protein were measured and found not to correlate. Rather, the statement simply acknowledges that Jang did not attempt to correlate mRNA and protein levels, and thus further research would be required to do so.

Instead of supporting the Examiner's assertion that there is no general correlation between mRNA and protein levels, Jang's conclusions actually support Applicants' position that there is such a general correlation. In light of the finding that there is no correlation between metastatic potential and mRNA levels for the genes measured, Jang concludes that, "these results suggest that the products of most of the genes studied may not be involved in the transient metastatic changes." See, Jang, Abstract. This conclusion impliedly assumes that, because the mRNA levels are not enhanced, the proteins levels are probably also not enhanced. It is in this context that Jang asserts that more studies are needed to determine if mRNA and protein levels correlate, in order to confirm the implicit assumption that an absence of enhanced mRNA expression probably denotes an absence of enhanced protein expression. Thus, Jang does not support the Examiner's position, and in fact supports Applicants' position.

According to the Examiner, the predictability of protein translation and its possible utility as a diagnostic are not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. The Examiner asserts that absent evidence of the protein's expression including the correlation to a disease state, one of skill in the art would be unable to predictably use the polypeptides in any diagnostic setting without undue experimentation.

As discussed above, it is more likely than not that the claimed polypeptides are differentially expressed in melanoma. The measurement of polypeptide levels involves standard techniques such as Western blotting or other immunoblotting technology. Thus, Applicants have

correlated the claimed polypeptides to a disease state and have enabled one of skill in the art to use the claimed polypeptides as diagnostic agents without undue experimentation.

For the foregoing reasons, Applicants maintain that one of skill in the art would be able to make and use the claimed polypeptides using the guidance provided in the specification. Accordingly, Applicants respectfully request that the enablement rejection be withdrawn.

Conclusion

The present application is believed to be in condition for allowance, and an early action to that effect is respectfully solicited. Applicants invite the Examiner to call the undersigned if any issues may be resolved through a telephonic conversation.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: April 29, 2005

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